REMARKS

Applicants submit this response to the Office Action mailed December 4, 2002. Claims 1-60 are pending, of which claims 12-18 and 22 are under examination. Claims 12-18 have been amended and claims 61-65 are added. New claims 61-65 are supported by the specification at, for example, page 8, lines 4-7, and Example 2. The amendment to claims 12-14 is supported at, for example, page 9, lines 16-24 and page 13, lines 6-9. The amendment to claims 15-18 is supported at, for example, page 30, lines 21-25 (claim 15), and page 30, lines 15-25 (claims 16-18). Care has been taken so that no new matter has been added. The response is formatted as numbered paragraphs to correspond to the paragraphs in the Office Action.

On Form 1449, received in the U.S. Patent and Trademark Office on February 20, 2002, it was noted that pages 246-248 of document AP were missing. A complete copy of document AP, *Nature Genetics* 26:345-348 (2000), is filed herewith along with PTO/SB/08A substituted for 1449/PTO form. Applicants request that the Examiner consider this document and make it of record in the application.

1, 2. Status of Application, Amendments, and claims

The Examiner's comments are acknowledged.

3. The requested amendment to the Brief Description of the Drawings has been made herein.

4. The requested addition of sequence identifiers has been made by amendment herein, and a new sequence listing is filed herewith.

5. The title has been amended herein.

6, 7. A new Abstract of the Disclosure is submitted herewith.

8, 9. Rejection under 35 U.S.C. § 101, non-statutory subject matter

Claims 15-18 are rejected under 35 U.S.C. § 101 as allegedly failing to include limitations to distinguish the claimed proteins, peptides and compositions from those that occur in nature. Without acquiescing to the ground of rejection, applicants have amended claims 15-18 to clarify that the claimed epitope-bearing region is comprised by an amino acid sequence. The language is supported in the specification including, for example, at page 30, lines 15-25, and page 31, lines 3-10. Reconsideration and withdrawal of this rejection are respectfully requested.

10. Rejection under 35 U.S.C. § 101, utility

Claims 12-18 and 22 stand rejected under 35 U.S.C. § 101 for allegedly failing to be supported by "an apparent disclosed specific or substantial credible utility." More specifically, the Examiner asserts that the application allegedly does not disclose the biological role of the nucleic acid, the encoded protein, or the significance of either.

Applicants respectfully traverse this ground of rejection. An applicant's assertion of utility in the disclosure is presumed to be correct. *See, e.g., In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Furthermore, only one specific, substantial and credible utility is required to satisfy the statutory requirement of 35 U.S.C. § 101. *Utility Examination Guidelines*, 66 Fed. Reg. 1092, 1097 (2001). The above guidelines state that the specific and substantial utility precludes "throw-away," "insubstantial," or "nonspecific" utility. Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and other evidence of record. *Id.*, at 1098. A claimed invention must be totally inoperative to lack credible utility. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Applicants respectfully submit that the claimed invention has a specific utility. Unlike the situation described in MPEP 2107.01, page 2100-32, where an assertion is made that "the compound might be useful in treating an *unspecified disorder*," (emphasis added) the instant claimed invention is to a member of the human FGF family, and these proteins are known to play important roles in regulation of cell metabolism, tissue growth, and differentiation. This is not a situation where a general statement of diagnostic utility, such as diagnosis of an unspecified disease, is made. MPEP 2107.01. Rather, the instant claimed invention discloses a specific utility in that the FGF-23 of the invention is cleaved during expression, resulting in production of a 20 kDa protein and a 7-12 kDa protein (page 7, lines 22-25). "The cleavage may play a role in

disorders of phosphate metabolism," (page 7, lines 28-29). The specification discloses that an FGF-23 that has been mutated to alter or delete the cleavage site provides a composition for treating disorders of phosphate metabolism, wherein the disorder is a result of cleavage of FGF-23 (page 8, lines 1-4). Such mutation is unique to FGF-23, according to a publication cited at page 7, lines 28-29 of the specification. Specifically, as indicated in *Nature Genetics* 26:245-48 (2000) at page 247, sentence bridging columns one and two: "Although the FGF family is extensive, discovery of mutations in an FGF besides *FGF23* has not been described in humans."

Thus, the specification and art cited therein together support the distinct nature of FGF-23 and a biological role thereof. The cited publication is of record (Information Disclosure Statement dated January 18, 2002) and a copy is filed herewith. [As indicated above, the P.T.O. noted that an incomplete copy was received, and a complete copy is filed herewith.]

Applicants submit that the claimed invention has a credible utility. "Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being 'wrong.'" *Revised Utility Examination Training Materials, http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf, pg. 5.* Further, "a credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use." *Id.* The applicants disclose that the claimed invention can be used to generate non-cleavable FGF-23 protein that is used to treat disorders of phosphate metabolism (page 8, lines 1-4). This credible utility cannot simply be dismissed as wrong. Therefore, the applicants respectfully assert that the claimed invention has a credible utility.

The Examiner further stated that, "There is no evidence of record that the claimed protein and/or compositions would have any activity that would result in the treatment of any disease or condition asserted in the instant specification." (Page 7, lines 3-5.) Applicants submit that the evidence presented in the specification is adequate to meet the utility requirement. However, in order to advance the prosecution of the application, applicants submit herewith a Declaration under 37 C.F.R. § 1.132 of Dr. Michael Kavanaugh. As indicated in the Declaration and the *Curriculum Vitae* of Dr. Kavanaugh, the Declarant is an internationally recognized expert in the area of protein chemistry, with particular emphasis in growth factors including FGF. Dr. Kavanaugh's publications have appeared in major peer-reviewed journals, and he is

qualified to provide and interpret data in support of the statements in the specification relating to utility of the claimed invention.

In his Declaration, Dr. Kavanaugh describes experiments in which mice were treated with non-cleavable FGF-23. In this non-cleavable form, glutamine replaces arginine at position 179. As indicated in paragraph 8 of the Declaration, a cleavage site in FGF-23 exists between position 179 and 180. This is also disclosed in detail in the present application at page 8, lines 1-7, and pages 39-40 (Example 2). Dr. Kavanaugh states in paragraph 13 of the Declaration that "systemically administered non-cleavable FGF-23 (R179Q) acutely and specifically lowers serum phosphate levels in mice." The Declaration also discusses experiments in which the time course of this effect of FGF-23 R179Q was measured, and these results are disclosed in paragraphs 14 and 15 of the Declaration. Tables of data supporting these conclusions are also presented in the Declaration.

Dr. Kavanaugh further explains how the data in the specification and in Tables 1 and 2 of the Declaration further elucidate recent information published by others suggesting a role of FGF-23 mutations in hereditary human diseases of bone metabolism. In one such case, the non-cleavable form of FGF-23 used in these studies in analogous to a mutated form of FGF-23 that has been associated with an inherited disease in humans, resulting in hypophosphatemia. This disease is discussed in a publication by The ADHR Consortium, *Nature Genetics* 26:345-248, 2000. As indicated above, this publication is of record in the patent application at page 7, lines 28-29, and in the Information Disclosure Statement filed on January 18, 2002, as document AP, and a copy is attached hereto.

These biological activities are specific characteristics of FGF-23 and provide a practitioner in this art with a reason for specifically choosing FGF-23 from among the family of FGF proteins. (As indicated above, the *Nature Genetics* publication states that FGF-23 is the only FGF protein shown to date to exhibit a mutation that relates to a human disease.) The claims meet the utility guidelines as follows:

- The utility is credible, in that it is a utility expected for a protein of this class, as borne out by experimental evidence provided and interpreted by one of skill in this art.
- The utility is specific, in that it is possessed by FGF-23 as a function of the characteristic amino acid sequence of FGF-23 and mutations thereof.

- The utility is substantial, in that FGF-23 has biological activity relevant to a physiological process (phosphate metabolism) that has pathological implications and is therefore relevant in developing methods of treating disease, including cancer, by modulating FGF-23 activity. This activity was clearly contemplated in the patent application as filed. See, for example, page 8, lines 1-4: "The invention provides compositions and methods for treating disorders of phosphate metabolism, wherein the disorder is a result of cleavage of FGF-23. The composition can comprise an FGF-23, or a polynucleotide encoding FGF-23, wherein the FGF-23 has been mutated to alter or delete the cleavage site."

In view of the foregoing remarks, applicants submit that the ground of rejection under 35 U.S.C. § 101 has been overcome. Withdrawal of this rejection is respectfully requested.

11, 12. Claim Rejections under 35 U.S.C. § 112, First Paragraph, utility

Claims 12-18 and 22 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly being non-enabled. The Action refers to the reasons for the rejections set forth under 35 U.S.C. § 101.

In view of the above remarks related to the rejection under 35 U.S.C. § 101, applicants submit that this ground of rejection under 35 U.S.C. § 112, first paragraph, has been overcome. Withdrawal of this rejection is respectfully requested.

13. Claim Rejections under 35 U.S.C. § 112, First Paragraph, written description

Claims 12, 13 and 22 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicants submit that claims 12, 13 and 22 as amended are not subject to this ground of rejection as the claims meet the requirements for written description as described by the Examiner. In particular, the specification and claims recite structural features common to the genus. At page 9, line 16, to page 10, line 24, the specification discloses growth factors having the biological activity of FGF-23, and a specified degree of homology. These proteins and

polypeptides share the *structural features* of a protein having the amino acid sequence of SEQ ID NO:4, in that the structure dictates the activity as measured using the methods as described and claimed (biological activity of the FGF-23, for example as disclosed in the specification and further discussed in the Declaration of Dr. Kavanaugh, filed herewith).

In view of the above remarks and the amendment to claims 12 and 13, Applicants submit that this ground of rejection under 35 U.S.C. § 112, first paragraph, has been overcome. Withdrawal of this rejection is respectfully requested.

14-15. Claim Rejections under 35 U.S.C. §112, second paragraph

Claims 12-14 and 22 are rejected under 35 U.S.C. §112, second paragraph. First, claims 12-14 and 22 are rejected in view of the recitation of "amino acids from about 1 to about 251," because allegedly the metes and bounds of "about" cannot be determined from the claims. Without acquiescing to the ground of rejection, the claims have been amended and applicants submit that they are no longer subject to this ground of rejection.

Further, claim 12 is rejected in view of the "95% identical" language. Applicants submit that this ground of rejection has been addressed in amended claim 12, which recites that the polypeptide retains the biological activity of human FGF-23, as supported in the specification at page 9, lines 16-24, for example.

Finally, claim 13 is rejected in view of the recitation of "conservative amino acid substitution." The word "conservative" clearly modifies the term "amino acid substitution" and applicants submit that one of skill in the art would understand the meaning, which is further supported in the specification at page 10, lines 23-24.

16-17. Claim Rejections under 35 U.S.C. § 102(b)

Claim 13 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Smallwood et al. (*Proc. Natl. Acad. Sci. USA* 93:9850-9857, 1996).

The Examiner has not asserted that Smallwood teaches a protein that is disclosed as FGF-23 in the present application, nor a protein having the biological activity of FGF-23. In

view of the amendment to claim 13, applicants submit that this rejection under 35 U.S.C. § 102(b) has been overcome. Withdrawal of this rejection is respectfully requested.

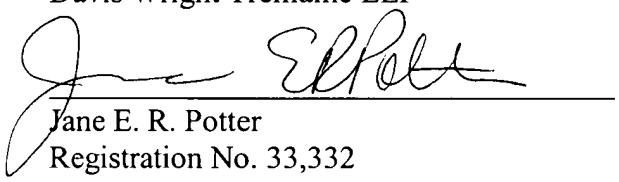
18. Claim 15 is rejected under 35 U.S.C. § 102(b) as being anticipated by Mahmood et al., *Development* 121:1399-1410, 1995. Without acquiescing to the ground of rejection, claim 15 has been amended and applicants submit that it is no longer subject to this ground of rejection.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,

Davis Wright Tremaine LLP



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Version With Markings to Show Changes

In the Claims:

The claims below have been amended as follows:

12. (Amended) An isolated polypeptide [comprising amino acids at least 95% identical to amino acids selected from the group consisting of:], the amino acid sequence of which comprises a sequence at least 95% identical to

[(a)] amino acids from [about] 1 to [about] 251 of SEQ ID NO:4[;

(b) amino acids from about 2 to about 251 of SEQ ID NO:4;

(c) amino acids from about 1 to about 24 of SEQ ID NO:4;

(d) amino acids from about 25 to about 251 of SEQ ID NO:4;

(e) amino acids from about 1 to about 175 of SEQ ID NO:4;

(f) amino acids from about 1 to about 177 of SEQ ID NO:4;

(g) amino acids from about 177 to about 251 of SEQ ID NO:4; and

(h) amino acids from about 180 to about 251 of SEQ ID NO:4], wherein said polypeptide retains the biological activity of native human FGF-23.

13. (Amended) An isolated polypeptide [wherein, except for at least one conservative amino acid substitution, said polypeptide has an amino acid sequence selected from the group consisting of:], the amino acid sequence of which comprises

[(a)] amino acids from [about] 1 to [about] 251 of SEQ ID NO:4[;

(b) amino acids from about 2 to about 251 of SEQ ID NO:4;

(c) amino acids from about 1 to about 24 of SEQ ID NO:4;

(d) amino acids from about 25 to about 251 of SEQ ID NO:4;

(e) amino acids from about 1 to about 175 of SEQ ID NO:4;

(f) amino acids from about 1 to about 177 of SEQ ID NO:4;

(g) amino acids from about 177 to about 251 of SEQ ID NO:4; and

(h) amino acids from about 180 to about 251 of SEQ ID NO:4], wherein at least one amino acid differs by conservative substitution from the corresponding position in SEQ ID NO:4, wherein said polypeptide retains the biological activity of native human FGF-23.

14. (Amended) An isolated polypeptide, the amino acid sequence of which comprises [comprising amino acids selected from the group consisting of]:

[(a)] amino acids from [about] 1 to [about] 251 of SEQ ID NO:4[;

(b) amino acids from about 2 to about 251 of SEQ ID NO:4;

(c) amino acids from about 1 to about 24 of SEQ ID NO:4;

(d) amino acids from about 25 to about 251 of SEQ ID NO:4;

(e) amino acids from about 1 to about 175 of SEQ ID NO:4;

(f) amino acids from about 1 to about 177 of SEQ ID NO:4;

(g) amino acids from about 177 to about 251 of SEQ ID NO:4; and

(h) amino acids from about 180 to about 251 of SEQ ID NO:4].

15. An amino acid sequence comprising an epitope-bearing portion of the polypeptide of SEQ ID NO:4 , wherein said epitope-bearing portion comprises at least 14 contiguous amino acids of SEQ ID NO:4.

16. The amino acid sequence[epitope-bearing portion] of claim 15, wherein said epitope-bearing portion [of claim 15, which] comprises between 10 and 50 contiguous amino acids of SEQ ID NO:4.

17. The amino acid sequence [epitope-bearing portion] of claim 15, wherein said epitope-bearing portion [of claim 15, which] comprises amino acids RRHTRSAEDDSERD (SEQ ID NO:19).

18. The amino acid sequence [epitope-bearing portion] of claim 15, wherein said epitope-bearing portion [of claim 15, which] comprises amino acids YHLQIHKNGHVDGAPHQ (SEQ ID NO:20).

Claims 61-65 are added.